

LONG-TERM ABSTINENT ALCOHOLICS HAVE A BLUNTED BLOOD GLUCOSE RESPONSE TO 2-DEOXY-D-GLUCOSE

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Abstract — **Aims:** In this study we explored the relationship between alcohol and carbohydrate consumption in long-term abstinent alcoholics. **Methods:** We employed an established laboratory paradigm which allowed us to stimulate and measure dietary intake. 2-Deoxy-D-glucose (2-DG) is a glucose analogue that causes an intracellular energy deprivation resulting in exaggerated food consumption and a compensatory metabolic response to raise blood glucose. Using a double-blind design, we gave an infusion of 25 mg/kg 2-DG or placebo to 20 long-term abstinent alcoholics and 19 healthy volunteers. **Results:** There were no baseline differences in any dietary, behavioural or biochemical variables. As expected, 2-DG increased caloric consumption and blood glucose levels in a time-dependent fashion. There were no differences in food consumption between the alcoholics and the healthy volunteers following the 2-DG stimulus. However, the alcoholic group had a significantly blunted response in blood glucose. **Conclusions:** The origin of this atypical blood glucose response may antedate the onset of alcoholism, or it may be secondary to alcohol-related damage that persists beyond 6 months. Previous accounts of increased sweet consumption in alcoholics were not substantiated, although they may be present in the peri-withdrawal period.

INTRODUCTION

Sober alcoholics frequently report that they binge on sweets to decrease their desire to drink alcohol (Anonymous, 1975). This exaggerated desire for sweets (Schuman *et al.*, 1987; Kampov-Polevoy *et al.*, 1999, 2001) has contributed to the postulate that alcohol consumption is regulated by the same mechanisms that regulate the intake of carbohydrates (Forsander, 1994).

The link between alcohol and carbohydrate consumption is supported by a number of studies. Human dietary studies show an inverse relationship between the consumption of carbohydrate and the intake of alcohol (Bresard and Chalbert, 1963; Eddy *et al.*, 1971; Yung *et al.*, 1983; Herbeth *et al.*, 1988; Colditz *et al.*, 1991). Animal studies show that the sum of the calories from food and alcohol remains constant when the diet is experimentally varied. At the neurochemical level, the same neuromodulator systems that influence gluoregulatory processes also influence alcohol intake (Grupp *et al.*, 1997a). Agents (e.g. naltrexone, isoproterenol, furosemide, 8 OH-DPAT, insulin zinc protamine, glibenclamide and angiotensin II) that have been shown in animals to modulate alcohol intake also modulate blood glucose (Grupp and Harding, 1996); the reduction in alcohol intake induced by some of these agents has been related to their effect on glucose availability (Grupp *et al.*, 1997a,b, 1998).

If a common mechanism regulates carbohydrate and alcohol consumption, then subjects with abnormal alcohol consumption (i.e. alcoholics) might be expected to exhibit abnormalities in carbohydrate regulation (Roach and Williams, 1966). Although studies have rarely explored dietary measures in alcoholics, blood glucose has been frequently studied, and

abnormalities have been found. Alcoholics have been shown to have an increased baseline glucose production rate (Bunout *et al.*, 1989), insulin resistance (Iturriaga *et al.*, 1986), abnormal glucose tolerance (Hed *et al.*, 1968; Sereny *et al.*, 1975; Adner and Nygren, 1990; Piccardo *et al.*, 1994; Greenhouse and Lardinois, 1996), and decreased utilization of glucose (Yki-Jarvinen and Nikkila, 1985).

There are several possible causes for the abnormal glucose regulation seen in previous studies of alcoholics. First, the changes may represent an inherited abnormality in glucose regulation that may be associated with a predisposition to develop alcoholism. Second, the abnormal glucose regulation may result from a permanent, damage effect on the body from long-term alcohol consumption. Third, since these studies have been conducted with recently detoxified alcoholics, the findings of abnormal glucose regulation may be due to the transient, toxic effects of alcohol on cellular processes affecting glucose homeostasis [e.g. to the pancreas (Geokas, 1984) and liver (Preedy *et al.*, 1997)]. Studies involving long-term, rather than recently detoxified, alcoholics could be expected to avoid the potential confounding effect caused by alcohol.

If there is a common mechanism regulating alcohol and carbohydrate consumption, we speculate that alcoholics have an abnormality in this mechanism manifested by increased carbohydrate consumption at times when they are not drinking. In order to explore this possibility by accurately quantifying carbohydrate consumption, we employed 2-deoxy-D-glucose (2-DG) in an established laboratory paradigm that stimulates dietary intake (Thompson and Campbell, 1977; Welle *et al.*, 1980; Breier, 1989; George *et al.*, 1994). Two-DG is a non-metabolizable analogue of glucose that inhibits glucose-6-phosphate dehydrogenase, blocks the breakdown of glucose and the production of ATP, and causes intracellular gluco-privation (Brown, 1962). 2-DG activates the hypothalamus (the area of the brain responsible for macronutrient selection), inducing hunger and causing an increased consumption of carbohydrate. The magnitude of the effect of 2-DG can be quantified with metabolic measures, such as the compensatory

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rise in peripheral circulating glucose. This increase in blood glucose occurs via direct autonomic innervation of the liver (i.e. promoting glycogenolysis and an increase in the outflow of glucose) as well as via increased glucagon and adrenaline secretion (Matsunaga *et al.*, 1989).

We hypothesized in the present work that, at baseline and following an infusion of 2-DG, alcoholics would consume more carbohydrate than non-alcoholic controls. We also hypothesized that this 2-DG stimulus would stimulate the desire of the alcoholics to consume alcohol. To quantify the effective stimulus of the 2-DG infusion in each group, we monitored the compensatory metabolic response in the plasma concentrations of glucose, insulin and glucagon.

SUBJECTS AND METHODS

Subjects

Twenty male alcoholics, abstinent for >6 months, participated in the study. Alcoholics were recruited through local Alcoholics Anonymous groups. Verification of an individual's sobriety was obtained from significant others and Alcoholics Anonymous sponsors. Nineteen male healthy volunteers, as well as alcoholics, underwent an extensive physical examination, including electrocardiogram (ECG), to insure that they were in good physical health. All subjects had normal liver function tests and normal fasting blood sugars. Subjects with a history of intravenous (i.v.) drug abuse, schizophrenia, bipolar disorder, or organic brain dysfunction were excluded from the study. All subjects were medication-free for at least 3 weeks prior to the study and had negative breath alcohol tests and negative urine drug screens. Alcoholics had abstained from alcohol consumption for at least 6 months. The NIAAA intramural research program Institutional Review Board approved the protocol, and written informed consent was obtained from each subject in accordance with the Declaration of Helsinki of the World Medical Association. Subjects were reimbursed for their participation.

Drinking history was determined for each subject, using a structured research questionnaire (Eckardt *et al.*, 1978). Psychiatric diagnoses were derived using the Structured Clinical Interview DSM-III-R (Mazure and Gershon, 1979), which was administered by a social worker with extensive training in diagnostic interviewing. All alcoholics fulfilled DSM-III-R criteria (American Psychiatric Association, 1987) for past alcohol dependence. Nine alcoholics met DSM-III-R criteria for past drug abuse or dependence. Some healthy volunteers drank alcohol socially, but none fulfilled DSM-III-R criteria for alcoholism, depression or any Axis I diagnosis. Healthy volunteers had a negative family history in first-degree relatives for significant alcohol abuse or dependence in parents or siblings.

Procedure

Following an overnight fast in the hospital, patients remained at bed rest and were given an i.v. line in the forearm. This line was kept open with a slow infusion of saline for a stabilization period of 1 h. At approximately 09:30, each subject received a continuous i.v. infusion for 30 min of either 25 mg/kg of 2-DG in 100 ml of normal saline or a placebo of 100 ml of normal saline. The two infusions were administered

according to a random-ordered double-blind design, separated by ≤ 7 days and ≥ 48 h. The intent in utilizing this dose of 2-DG was to induce dietary changes with few other physiological effects (George *et al.*, 1994).

Biochemical variables

To obtain blood for biochemical analysis, samples were drawn through the i.v. line at baseline and at 60, 90, 120 and 150 min after the beginning of the infusion. Blood for glucose was collected in tubes containing potassium oxalate/sodium fluoride, and were sent immediately to the Clinical Pathology Department of the National Institutes of Health Clinical Center for photometric assay with hexokinase. Blood for glucagon was collected in tubes containing Trazilol and EDTA. Blood for insulin was collected in a separate serum separation tube. These samples were immediately placed on wet ice, centrifuged, aliquoted, and stored at -80°C prior to analysis. Covance Laboratory in Vienna (VA, USA) performed the analyses. Insulin was assayed using a TOSOH (San Francisco, CA, USA) enzyme-linked immunosorbent assay and had a 4.6% inter-assay variation. Glucagon was assayed using radioimmunoassay and had a 5.5% inter-assay variation.

Physiological variables

Blood pressure (BP) and pulse rate were measured from the non-dominant arm using a Dinamap automated BP cuff (Critikon Co., Tampa, FL, USA). Vitals signs were determined at baseline, and 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 135, 150, 165, 180 and 240 min after the beginning of the infusion. The subjects' temperature and ECG were also monitored to safeguard against any abnormalities during the study.

Test meal

Following the 150-min blood draw, subjects ate *ad libitum* from a specially prepared and carefully quantified lunch tray provided by the National Institutes of Health Nutrition Department's Metabolic Kitchen. By measuring the food and beverage consumed from this quantified lunch tray, the Nutrition Department staff calculated the total amount of carbohydrate, fat, protein, and kilocalories consumed by each subject.

Urge to Drink Alcohol Questionnaire

The Urge to Drink Alcohol Questionnaire was adapted, with permission, from the Questionnaire of Smoking Urges (Tiffany and Drobes, 1991), to reflect alcohol use. The questionnaire consists of 32 items, assessing four categories: desire to drink; intention to drink; anticipation of positive outcome; and anticipation of relief from withdrawal or negative state. Each of these categories consists of eight items from the scale. This self-report instrument was obtained at baseline and at 150, 180 and 240 min following the infusion. Subjects completed the scales based on how they felt at the height of the infusion at 150 min, and at 180 and 240 min, based on how they felt since the previous time they had completed the instrument.

Statistical analysis

The statistical package used for all analyses was Statistica by Statsoft (Tulsa, OK, USA). Tests utilized included analysis of variance, multiple analysis of variance, and correlations. A significance level of $P = 0.01$ was selected, because of the number of tests performed. Results are expressed as means \pm SD.

RESULTS

There was no difference between the groups for age, liver function tests, or anthropomorphic measures (Table 1). Alcoholics had a prior history of 10.9 ± 7.8 years (mean \pm SD) of heavy alcohol consumption, and an average of 26.1 ± 25.3 months of abstinence from alcohol prior to the study. All alcoholics were abstinent for at least 6 months prior to the study. Alcoholics were significantly different from healthy volunteers on all of the drinking variables we measured. Correlational analyses indicated that the length of time that the alcoholics had abstained from alcohol was not related to any of the dependent variables (e.g. glucose, insulin, glucagon, food consumption, and urge to drink questionnaire). Similarly, the history of previous drug use (including marijuana) was not related to any dependent variable. Among the 19 healthy volunteers, seven were non-drinkers. The other 12 were social drinkers who averaged one drinking occasion per week that consisted of, on average, two alcoholic drinks on each occasion. Alcoholics smoked significantly more cigarettes per day than healthy volunteers (7.5 ± 11.8 and 0.8 ± 3.4 , respectively, $P < 0.01$).

Biochemical variables

The administration of 2-DG caused a significant increase in blood levels of insulin (Fig. 1), glucagon (Fig. 2), and glucose (Fig. 3). The maximum value for each of these three parameters was noted 90 min after the infusion. There was a significant interaction between drug (2-DG) and time for insulin [$F(3,87) = 16.21$, $P < 0.001$]. There was a significant main effect of drug for glucagon [$F(1,33) = 36.65$, $P < 0.001$]. Compared to the healthy volunteers, alcoholics had a significantly blunted blood glucose response to 2-DG (Fig. 3), noted by the significant three-way interaction between drug, time and group [$F(3,111) = 70.56$, $P = 0.001$]. *Post hoc* comparisons between alcoholics and healthy volunteers were performed for each time point on both the drug and placebo days. There were group distinctions following 2-DG: $t = 60$, $F(1,37) = 5.11$, $P = 0.03$; $t = 90$, $F(1,37) = 5.22$, $P = 0.03$; $t = 120$, $F(1,37) = 5.88$, $P = 0.02$; $t = 150$, $F(1,37) = 9.41$, $P = 0.004$. The groups were similar following placebo: $t = 60$, $F(1,37) = 0.28$, $P = 0.60$; $t = 90$, $F(1,37) = 0.04$, $P = 0.84$; $t = 120$, $F(1,37) = 0.26$, $P = 0.62$; $t = 150$, $F(1,37) = 0.16$, $P = 0.69$. After Bonferroni correction, the differences were only statistically significant for glucose at 150 min after the infusion (Fig. 3). Considering that the blunted blood glucose response noted in alcoholics might possibly be related to their increased use of cigarettes, smoking and non-smoking alcoholics were evaluated separately. The 10 smoking alcoholics and 10 non-smoking alcoholics were compared, and their blood glucose

Table 1. Anthropomorphic measures of alcoholics and healthy volunteers

Parameter	Alcoholics (n = 20)	Healthy volunteers (n = 19)
Height (cm)	177 \pm 8.38	178 \pm 7.26
Weight (kg)	80.3 \pm 17.2	82.4 \pm 10.8
Body mass index (kg/m ²)	25.4 \pm 3.69	25.9 \pm 2.72

Values are means \pm SD.

There were no significant differences between groups on any of these measures.

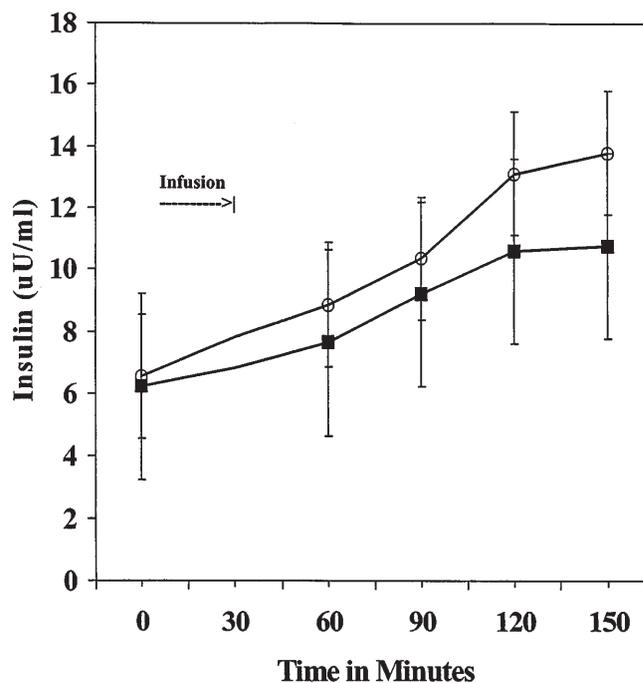


Fig. 1. Effect of 2-deoxy-D-glucose administration on insulin response in alcoholics (■) and healthy volunteers (○).

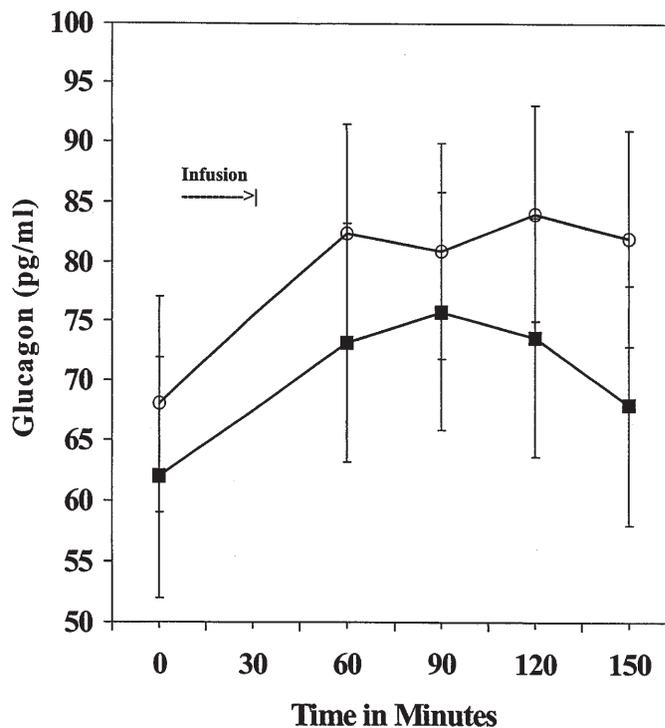


Fig. 2. Effect of 2-deoxy-D-glucose administrations on glucagon response in alcoholics (■) and healthy volunteers (○).

response to 2-DG was found to be similar [$F(1,18) = 1.00$, $P = 0.33$]. All of the biochemical variables examined (i.e. insulin, glucagon and glucose) revealed a blunted response to 2-DG when alcoholics were compared to healthy volunteers (Figs 1–3).

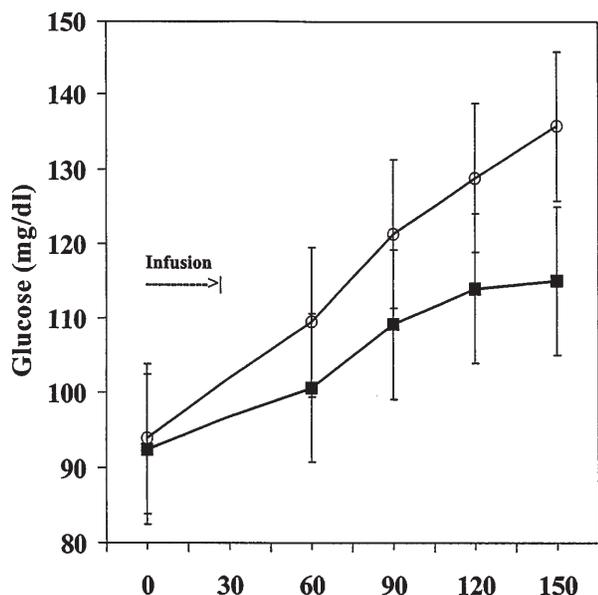


Fig. 3. Effect of 2-deoxy-D-glucose (2-DG) administration on blood glucose response in alcoholics (■) and healthy volunteers (○). There were significant group distinctions 150 min after the onset of the 2-DG infusion.

Physiological variables

There were no baseline differences between groups for systolic or diastolic blood pressure, or heart rate. On both days, temperature and systolic blood pressure increased over time [$F(15,345) = 7.43$, $P < 0.001$ and $F(15,435) = 17.18$, $P < 0.001$, respectively]. There were no significant drug or group effects. Following the 2-DG infusion, but not the placebo, diastolic blood pressure decreased over time [$F(15,435) = 8.28$, $P < 0.001$]. Similarly, there was a significant interaction between drug and time for heart rate, as heart rate increased following the meal [$F(15,435) = 3.98$, $P < 0.001$].

Test meal

Two-DG increased the consumption of carbohydrates and total calories in both alcoholics and healthy volunteers [$F(1,36) = 10.08$, $P = 0.003$ and $F(1,36) = 7.19$, $P = 0.01$, respectively]. There was no significant drug effect on the consumption of fat or protein, and there were no group effects on any of these dietary variables.

Urge to Drink Questionnaire

There were no differences between alcoholics and healthy volunteers at baseline for any of the subscales on the Urge to Drink Alcohol Questionnaire. Similarly, there were no drug, time, or group effects noted during the study.

DISCUSSION

To our knowledge, this is the first study in humans that has attempted to quantify carbohydrate consumption in long-term sober alcoholics. The study produced three major findings. First, alcoholics and controls had similar carbohydrate consumption at baseline and following 2-DG stimulation. Second,

2-DG did not induce an increased desire to drink alcohol. Third, alcoholics had a reduced blood glucose response following the 2-DG infusion. Alcoholics also exhibited trends towards blunted responses in glucagon and insulin.

The primary objective of this study was to explore carbohydrate consumption in alcoholics. Our interest in this area was generated by both clinical observations and reports in the Alcoholics Anonymous literature that sober alcoholics frequently consume excessive sweets. The fact that we did not find any difference in carbohydrate consumption between alcoholics and non-alcoholics at baseline or following 2-DG suggests that previous accounts about sweet consumption and alcoholics may be more applicable to the peri-withdrawal period of time and do not persist into long-term abstinence. The length of time spent in alcohol recovery may also have an important effect on the alcoholics' desire to drink alcohol, as measured by the Urge to Drink Questionnaire. Measures of actual alcohol consumption were not feasible.

The significance of the atypical glucose regulation (i.e. blunted blood glucose response) noted following 2-DG is not known. Although it is possible that such atypical glucose regulation precedes the onset of alcoholism, it is also possible that alcohol exposure causes this abnormality. A similar abnormality, that of a blunted glucose increase following insulin-induced hypoglycaemia, has been noted by Eisenhofer (1984) in a group of long-term abstinent alcoholics. All the subjects in this group displayed nervous system damage that was attributable to the effects of alcohol exposure. In one subject, who had no hormonal response at all, Eisenhofer (1984) attributed the defect in glucose regulation to alcohol's damaging effect on central glucoreceptors. Such damage to central glucoreceptors (i.e. in the hypothalamus) could be one mechanism for the depressed blood glucose response we noted following 2-DG administration. Specific neurons in the hypothalamus (i.e. vasoactive intestinal peptide neurons in the hypothalamic supra-chiasmatic nucleus) that are sensitive to damage from alcohol (Madeira *et al.*, 1997) also mediate the glucose elevation induced by 2-DG (Chun *et al.*, 1998). Permanent alcohol damage to other areas of the body, such as the adrenal medulla, might possibly contribute to the blunted response of the alcoholics. However, if a catecholamine defect was involved, then alcoholics might be expected to have an increased insulin response and increased cardiovascular markers of sympathetic activity (i.e. blood pressure and heart rate), but this did not occur. Other alcohol-associated changes may also contribute to the atypical blood glucose response to 2-DG noted in our study. However, there is little evidence that the peculiar metabolic characteristics and nutritional deficiencies which have been previously reported in alcoholics actually persist after 6 months of abstinence from alcohol (Gloria *et al.*, 1997; Addolorato *et al.*, 1998, 1999).

In summary, we did not find any evidence for increased carbohydrate consumption, at least in short-term experiments, in long-term abstinent alcoholics. However, we did find that long-term abstinent alcoholics have a blunted hyperglycaemic response after an infusion of 2-DG. The origin of the atypical response is unknown. This finding does, however, add another dimension to the theory that the regulation mechanisms of alcohol and glucose are related and are altered in alcoholics. In the future, 2-DG could be given to alcohol-naïve subjects who are at different degrees of risk of developing alcoholism.

Such a study could determine if our findings are indicative of carbohydrate regulatory abnormalities associated with a trait that predisposes an individual to become alcoholic, or if they are merely indicative of long-lasting alcohol-induced damage.

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